Study summary:
‘Analysis of the consequences of a cliff edge scenario in Brexit on the availability and regulatory oversight of pharmaceuticals and medical devices’

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1 Introduction and objective of the study

Following the June 2016 referendum in the United Kingdom of Great Britain and Northern Ireland (referred to below as the "UK"), and the enactment of Article 50 of the Treaty on European Union (EU), the UK will no longer be an EU Member State after 29 March 2019. The consequences of this unprecedented process ("Brexit") are complex for both the UK as well as for the remaining 27 EU Member States ("EU27"), which includes the Netherlands. Brexit is expected to impact overall trade, regulatory, surveillance and collaboration activities across industry sectors, including the Health & Life Sciences sector, with the potential to impact patients within the Dutch market.

Although Brexit will be effective in several months, the final and specific conditions that will underpin the interaction between UK and the EU27 as of 30 March 2019 are not yet confirmed. This study therefore focuses on the scenario where no agreement between UK and EU27 has been reached, i.e. a "cliff edge", "no deal", or so-called "hard Brexit", implying that the UK would become and be recognized as a third country as of 30 March 2019.

The objective of the study summarized in this document was to investigate main risks for patients in the Dutch health and life sciences ecosystem in the case of such a cliff edge Brexit scenario, related to:

- Pharmaceutical (also referred to Medicinal) Products,
- Medical Devices and In Vitro Diagnostics, and
- Medical Research.

The performed study focused on cliff edge Brexit consequences on the availability, safety and surveillance of medicinal products, medical devices and in vitro diagnostics in the Netherlands. Additionally, the consequences for Dutch medical research were analysed. By identifying and mapping pharmaceutical and medical device product streams between the UK and the Netherlands, processes and procedures around product import- and export, market access and surveillance, product trade and R&D value chains, and other UK/Netherlands interrelations and dependencies, the study aimed to provide insight into the potential consequences and risks to the Dutch health system under this cliff edge Brexit scenario. The results of the analysis allow the Ministry of Health, Welfare and Sport, as well as other relevant authorities and market stakeholders to take the most relevant precautionary measures to prepare for and mitigate any undesirable risks.

2 Framework

In order to obtain and/or keep market authorization on the Dutch and EU market, pharmaceutical products, medical devices (MD) or in vitro diagnostic devices (IVD) need to fulfill a broad series of legislative, directives and regulatory requirements. Also strict requirements are subjected before, during and after clinical trials: i.e. medical research studies in which the safety and efficacy of investigational medicinal products or medical device prototypes are thoroughly evaluated in humans, both in healthy volunteers and patients. Table 1 below describes the important requirements in relation to market access, surveillance and research of pharmaceutical, MD and IVD products in the Netherlands and the EU, particularly relevant in the context of a cliff edge Brexit.

Focus areas	Key regulatory requirements for market authorization, surveillance and (clinical) development of pharmaceutical, MD and IVD products:
Pharmaceutical Products	• Produced in compliance with Good Manufacturing Practices (GMP; GMP certificate validity of 3 years), which is considered to be confirmed through an inspection exercise performed by an EU inspectorate. • Be subject to quality control (QC, i.e. testing against its product specifications) on an EU approved site, and to batch release activities (BR) on the EU ground and by a Qualified Person (QP) based in EU, as per Directive 2001/83/EC. • Go through customs – in the case of a product transiting through third countries. • Be connected to a valid Marketing Authorization (MA), which can be obtained through centralized procedure (i.e. granted by the EMA) or decentralized procedure (i.e. granted by an EU Reference Member State (RMS)), as per Directive 2004/27/EC. • Have its Marketing Authorization Holder (MAH) based in the EU, as per Directive 2001/83/EC; • Be associated to a Qualified Person for Pharmacovigilance (QPPV) located in the EU, as per Regulation (EU) No 1235/2010 and Directive 2001/83/EC. • Have a Pharmacovigilance System Master File (PSMF) located in the EU, as per Directive 2010/84/EU, and more specifically at the location where main pharmacovigilance activities are performed or at the same location than the QPPV, as per Commission Implementing Regulation (EU) 520/2012.
Medical Devices and In Vitro Diagnostics	• An MD or IVD product on the EU (thus incl. NL) market should have been issued with a valid CE mark by a so-called Notified Body (NB). • NBs are companies authorized by the EU to carry out conformity assessments under the relevant EU Directives (93/42/EEC, 90/385/EEC and 98/79/EC) for MD, incl. active implantable medical device (AIMD), and IVD products. A NB conducts the conformity assessment against the relevant sections of the applicable EU Directive and executes the necessary quality assurance and product certification processes. • In order to realize valid CE markings, NBs need to be in or recognized by the EU, according to a formal notice to stakeholders 'Withdrawal of the United Kingdom and EU rules in the field of industrial products' on 22 January 2018 by the European Commission referring to Union product legislation. • The authorized representative (EC-REP) of a marketed MD or IVD product must be situated in the EU. • Import authorization is required for MD and IVD products from third countries. • The General Data Protection Regulation (GDPR) is applicable to the transfer and exchange of personal device and clinical data.
Medical Research	• A request for authorization of the clinical trial with investigational product batches, i.e. investigational medicinal product or a medical device clinical prototype, first needs to be assessed by a competent authority in the concerning EU Member State. In the Netherlands, clinical trial authorization submissions are assessed by one of the accredited medical research ethics committees (MRECs) and/or the CCMO. In the UK, this is coordinated by the MHRA. • GxP inspections, around Good Manufacturing (GMP), Good Laboratory (GLP) and Good Clinical Practices (GCP) should be performed by an EU inspectorate. • Import authorization is required for investigational product batches from third countries. • For investigational medicinal products, batch release is required to take place on EU ground by an EU based Qualified Person (QP). • The clinical study sponsor or legal representative needs to be based in the EU. • The General Data Protection Regulation (GDPR) is applicable to the transfer and exchange of clinical data. • For Market Authorization of new, innovative products, applicable requirements are identical to those described in the Pharmaceutical Products and Medical Devices and In Vitro Diagnostics sections of this table.

Table 1 – Relevant requirements for pharmaceutical products, medical devices & in vitro diagnostics, and medical research in the context of a cliff edge Brexit

3 Major risks

The requirements displayed in Table 1 are likely to be impacted by the UK no longer being recognized as an EU Member State as of the cliff edge Brexit date. When UK based organizations, such as regulatory bodies, companies or other stakeholders, play a role in fulfilling the requirements, sudden invalidation of the above requirements is possible.

Potential invalidation of these requirements induces a series of risks which can affect the supply, availability and safety of pharmaceutical products, MD, IVD and investigational products, potentially

impacting the Dutch patient population if no mitigating actions are proactively undertaken in advance of Brexit. In addition, Dutch companies, institutions and consortia performing clinical trial studies with UK partners and/or sponsors are also at risk of becoming noncompliant to one or several of the requirements in Table 1, ultimately leading to clinical trials getting significantly disrupted, delayed or (in worst case) terminated. This could limit market access and thus availability of innovative therapies to Dutch patients.

In this study, most important risks were identified for pharmaceutical products, medical devices and in vitro diagnostic products, and medical research. Risks that were considered as of the highest importance based on probability of occurrence, acuteness and impact, are listed in Table 2 below.

Focus areas	High priority, short term risks as a result of a cliff edge Brexit
Pharmaceutical Products	• Products with physical entry in the EU27 via the UK Products transiting through UK will have to undergo customs inspections. This may lead to additional supply delays, especially in case actors do not foresee this impact in their supply chain planning activities. The highest risk stands for products where supply chain is tightly managed (e.g. refrigerated products) and with smaller players, which do not necessarily have the capacity to anticipate these changes (e.g. through adequate planning or stockpiling). • Products whose quality control (QC) testing & batch release (BR) activities taking place in the UK All products with QC & BR activities located in the UK will have to undergo QC & BR activities in an EU27 location to be marketed in EU27. This is expected to induce changes in the supply chain (e.g. product to be re-routed to have QC activities on another site) and in the overall talent sourcing approach (i.e. for Qualified Person (QP)); and might lead to product unavailability if these risks are not mitigated (reinforced in the case of changes requiring long lead-time MA variations). • Products whose MAH is a UK-based entity All products whose MAH is a UK-based legal entity will have to be associated to an EU27-based legal entity to be marketed in EU27. Although this can easily be mitigated by large players with multi-site presence in EU27, smaller player might need to set-up an additional LE in EU27 or to include additional partners in their distribution approach to be able to serve the EU27 market. Inability to comply with these requirements might then lead to product unavailability.
Medical Devices and In Vitro Diagnostics	• MD and IVD certified by UK notified bodies After 29 March 2019, the EU no longer acknowledges UK notified bodies in the case of a cliff edge Brexit, and certificates by UK NBs are not recognized. All MDs and IVDs certified by a UK NB would now need to undergo a certification procedure with an EU27 NB, resulting in the risk of not being authorized for marketing on the Dutch and EU market in case of non-compliance or incomplete certification procedures at the alternative EU NBs. In any case, all MD and IVD products requiring a certificate should not rely on an UK NB in case of an expected issuance after 29 March 2019. The risk should also be considered for IT products which fall in the category of MD, specifically because each new software version requires a new certification. • MD and IVD potentially impacted by limited EU27 notified bodies capacity All certification workload, which is currently covered by UK NBs will have to be covered by EU27 NBs (except for MDs and IVDs, which were certified in the UK and dedicated to the UK market only). UK NBs that want to continue to play a role in EU certifications of MDs and IVDs need to relocate to the EU and obtain an EU27 NB designation (already observed for various UK NBs, such as BSI). The additional Brexit related workload will be added to existing capacity pressures experienced by EU NBs related to the implementation of the new EU regulations on medical devices and in vitro diagnostics (EU 2017/745 and EU 2017/746). This joint workload increase might induce additional delays in the certification process and increase time-to-market for certain MD and IVD products.
Medical Research	• Clinical trials with products transiting through UK or with BR activities performed in the UK All investigational medicinal products (IMPs) and MD or IVD prototypes used in EU27 clinical trials that transit through the UK will have to undergo customs inspections. In addition, after a cliff edge Brexit, IMPs with BR activities in the UK will now also have to undergo BR activities in an EU27 location by an EU27 based QP. Similarly to marketed pharmaceutical products, these requirements might lead to additional supply delays or to product unavailability, which could then disturb clinical trial planning, delay or in worst case lead to termination of a clinical trial.

Table 2 - Major cliff edge Brexit risks regarding Pharmaceutical Products, Medical devices and In Vitro Diagnostics, and Medical Research

Next to the most acute risks displayed in Table 2, this study also revealed several minor and/or longer term risks related to:

- Other regulatory processes prior to, during and after clinical trials (besides the availability risk for investigational products mentioned in Table 2).
- Mandatory appointment of an EU Qualified Person for Pharmacovigilance (QPPV).
- EU27 inspectorate capacities.
- Supply chain, logistics and customs requirements for MD and IVD products.
- The EU General Data Protection Regulation (GDPR) applicable to the transfer and exchange of clinical and personal device data.
- Authorized representatives for MD and IVD products to be appointed in the EU.
- UK/Netherlands R&D collaboration, funding opportunities, and research excellence.

In the context of the assessment presented above, a series of items should be considered as they impact the overall risk levels and probability:

- What regards medicinal products, significant efforts have been (and are still being) undertaken by the European Medicines Agency (EMA) to ensure that all pharmaceutical products connected to a central marketing authorization can still be supplied in the EU27 in the case of a cliff edge Brexit. For nationally authorized products, similar efforts are being undertaken by the Heads of Medicines Agencies (HMA), the network of EU27 Medicines Evaluation Boards (MEBs; for the Netherlands: the CBG (College ter Beoordeling van Geneesmiddelen). A wide variety of press releases also suggest that major pharmaceutical industries and stakeholders have started their efforts for mitigating potential cliff edge Brexit risks.
- What regards MDs and IVDs, major medtech industries and other stakeholders have been communicating about ongoing efforts to reduce the impact of a potential cliff edge Brexit, e.g. by stock splitting across EU and UK, as well as supply chain optimization efforts. Furthermore, various UK NBs have been relocated to EU27 countries, including the Netherlands, in order to continue their business in EU certification of MD and IVD products. For instance, BSI (a UK based NB) recently achieved designation as a medical device NB in the Netherlands.
- Specific requirements and potential risks regarding raw materials, intermediate products, MD product parts were considered out of scope and were not further detailed. Similarly, all parallel trade related risks have been considered out of this study's scope.

4 Conclusion and final remarks

As highlighted in the previous section, key risks of a cliff edge Brexit on the Dutch healthcare and life sciences sector are primarily the result of a combination of 1) uncertainties in the post-Brexit regulatory framework and 2) supply chain, logistics and customs uncertainties. In summary, these key risks can mainly lead to delays and/or temporary limitations in availability of products and devices on the Dutch market, if appropriate mitigation actions are not undertaken. Simultaneously, it could hamper timely completion or in worst case lead to termination of specific Dutch clinical trials or Dutch sponsored clinical trials on UK sites.

Most of the described risks can be mitigated by commercial players (i.e. manufacturers, distributors, marketing authorization holders) through administrative changes or supply chain modification, likely leading to additional time efforts and costs. It is expected that larger players are already undertaking relevant actions, while smaller players will be less able to execute these contingency measures and should be subjected to specific awareness actions. Other risks are more connected to key regulatory bodies involved in the different processes, and will significantly depend on how these bodies tackle potential capacity issues and to what extent mitigating actions are undertaken. Examples of such mitigation actions

are to repetitively quantify expected capacity impact per regulatory body and deploy a plan for covering the additional workload, in the Netherlands, but preferably at EU27 level, in collaboration with other Member States.

The exact circumstances and outcomes of Brexit are currently unknown, the regulatory uncertainty is still high and a range of parameters are changing at an incredibly high pace. Major regulatory actors and bodies neither have a complete nor a final view on the regulatory frame that will be ultimately applicable. Despite this uncertainty, major players within the ecosystem are undertaking a range of actions to mitigate and tackle risks, with statistics on Brexit readiness that are expected to change from one day to another. As a result, it is imperative to continue to scan for additional legislation, regulatory changes or guidance, keep tracing the development and nuance of existing information, evaluate the impact on the market segment and conduct risk-based preparations for the worst likely scenarios to ensure continuity of product supply and quality of patient care.

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